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Interventional Bronchoscopy: State-of-the-Art Review

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Abstract

For over 150 years, bronchoscopy, especially flexible bronchoscopy, has been a mainstay for airway inspection, the diagnosis of airway lesions, therapeutic aspiration of airway secretions and transbronchial biopsy to diagnose parenchymal lung disorders. Its utility for the diagnosis of peripheral pulmonary nodules and therapeutic treatments besides aspiration of airway secretions, however, has been limited. Challenges to the wider use of flexible bronchoscopy have included difficulty in navigating to the lung periphery, the avoidance of vasculature structures when performing diagnostic biopsies and the ability to biopsy a lesion under direct visualization. The last 10-15 years has seen major advances in thoracic imaging, navigational platforms to direct the bronchoscopist to lung lesions and the ability to visualize lesions during biopsy. Moreover, multiple new techniques have either become recently available, or are currently being investigated to treat a broad range of airway and lung parenchymal diseases such as asthma, emphysema, chronic bronchitis or to alleviate recurrent exacerbations. New bronchoscopic therapies are also being investigated to not only diagnose, but possibly treat malignant peripheral lung nodules. As a result, flexible bronchoscopy is now able to provide a new and expanding armamentarium of diagnostic and therapeutic tools to treat patients with a variety of lung diseases. This state-of-the-art review succinctly reviews these techniques and provides clinicians an organized approach to their role in the diagnosis and treatment of a range of lung diseases.

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Introduction

For over 150 years, bronchoscopy has been instrumental in the inspection and diagnosis of airway and parenchymal lung diseases.(1) Recently, the capabilities of bronchoscopy to diagnose and treat a variety of lung diseases has expanded. Bronchoscope designs with enhanced optics, greater resolution, flexibility and smaller size but with functional working channels are key to these advances.

High-resolution chest CT (HRCT) imaging provides enhanced structural detail of lung lesions and coupled with navigational technology provides endoscopic roadmaps to small distal lesions. HRCT imaging can construct pulmonary vasculature maps and provide virtual avascular paths to lesions that lack a leading bronchus. Incorporation of real-time imaging during bronchoscopy can provide precision location of difficult to reach targets.

Simultaneously, advances in endobronchial ultrasound coupled with instruments that can aspirate, biopsy, cut, brush, freeze, ablate, and vaporize tissue provides an array of modalities to diagnose and treat many lung diseases. (Table 1)

Bronchoscopic interventions in selected patients with asthma and emphysema provides new treatment options. Current research focused on treating chronic bronchitis, fixed airflow obstruction and lung cancer offer the possibility of less invasive, but effective therapies. (Table 2)

Herein, we review recent advances in the diagnostic and therapeutic applications of bronchoscopy.

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Interventional bronchoscopy for lung cancer diagnosis and treatment

Modalities that enhance imaging and provide bronchoscopic navigation to lung lesions

Several imaging modalities can improve access to peripheral lesions. Some modalities provide real-time imaging during navigation (convex endobronchial ultrasound (EBUS), radial endobronchial ultrasound (rEBUS), fluoroscopy and CT imaging modalities); others use planning HRCTs to create navigational paths. A patient's condition during planning HRCT is different compared to the procedure; spontaneous respiration vs. intubation plus mechanical ventilation, anesthesia and paralysis, and higher inspired O_2, respectively. The latter results in atelectasis and creates CT-to-body divergence. CT-to-body divergence describes differences in targeted lesion locations identified pre-procedurally by HRCT and its location during bronchoscopy. CT-to-body divergence is more important than nodule size in adversely affecting diagnostic yield and a crucial barrier to ablation.(2) The following modalities have been developed to address this obstacle, however, it none of the technologies have been directly compared for diagnostic yields or cost-effectiveness.

Imaging techniques

Radial EBUS (rEBUS)

Launched in 1999, rEBUS (Olympus Cooperation, Tokyo, Japan) uses a flexible catheter and rotating ultrasound transducer to produce 360° ultrasound images, it was first used to guide transbronchial lung biopsy (TBLB) (3). During bronchoscopy, the 20-MHz mechanical probe is inserted through a guide sheath into the lung periphery. Figure 1 shows a typical ultrasonographic image.

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rEBUS is the most commonly used real-time technique to confirm a lesion during diagnosis and probe placement during therapeutic interventions. However, discordance has been reported for diagnostic yields amongst studies.

Steinfort (4) evaluated > 1,400 patients with rEBUS guided transbronchial biopsy and showed a specificity of 1.00 and sensitivity of 0.73 for lung cancer diagnoses. Variations in diagnostic sensitivities were attributed to the prevalence of malignancy, lesion size, probe position and use of fluoroscopy. In a multicentered controlled trial, the diagnostic yield of thin bronchoscope (TB) plus rEBUS was compared with standard bronchoscopy and fluoroscopy (SB-F); average lesion size was 31.2 $\pm$ 10.8 mm.(5) Diagnostic yield was higher with TB-rEBUS compared to SB-F (49% vs 37) but was not statistically significant.

Several reasons may explain differences in diagnostic yield bedside lesion characteristics. rEBUS probes are not steerable; navigation support might be useful especially in lesions < 2 cm. Eberhardt (6) reported that EBUS with electromagnetic navigational bronchoscopy (ENB) beneficially combines real-time imaging with steerability. Diagnostic yields of the combined procedure are greater than rEBUS or ENB alone. Others have confirmed this finding. (7). An opportunity exists to improve rEBUS imaging, especially semisolid lesions, to enhance diagnostic accuracy.(8)

Navigational techniques

ENB (electromagnetic navigational bronchoscopy)

ENB systems (Medtronic, Inc., Minneapolis, USA) assist placing biopsy tools into lesions. It uses low-frequency electromagnetic waves emitted from an electromagnetic board placed under the patient. A sensor probe is mounted on a cable tip and a flexible catheter provides biopsy tool access (9).

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Meta-analyses report diagnostic accuracies of 70-75%.(10-12). Lesion location, nodule size, an existing bronchus sign, procedural error and biopsy technique all affect diagnostic yield. a A prospective multicenter study (NAVIGATE) evaluated ENB using the superDimension navigation system (Medtronic, Minneapolis, MN) in patients with median nodule size 20 mm.(13) In 1,157 patients that underwent ENB, 94% had navigation completed; diagnostic yield was 73%. The system recently added tomosynthesis (serial x-rays images during c-arm rotation) to to improve real-time fluoroscopic evaluation and address CT-to body divergence.

The SPiN® Thoracic Navigation System (Veran Medical Technologies, Inc., St. Louis, USA) is an ENB platform that uses respiratory gating technology to track moving nodules during endoscopic or transthoracic lung nodule biopsy. (14) Biopsy instruments have electromagnetic sensors that guide and track the path to the target and also addresses CT-to-body divergence.

VBN (Virtual bronchoscopic navigation) and Augmented Fluoroscopy

Virtual bronchoscopic images of the bronchial path to a peripheral lesion are generated by software using HRCT data. During bronchoscopy, the virtual navigational image is projected on a display screen and compared to real-time images. Eberhardt (15) reported a 80% diagnostic yield in patients with solitary pulmonary nodules. Diagnostic yield with VBN depended upon lesion size, lobar location and bronchus sign presence.

Visual guidance to targeted lesion is superimposed onto the endoscopic image (LungPoint (Broncus Medical, Mountain View, California, USA). An image-based registration technique aligns virtual images with live bronchoscopic video. Once near the target, the lesion shape is overlaid onto the airway wall to provide biopsy guidance (Figure 2). Lesion shape is overlaid onto live fluoroscopic images (e.g., fused fluoroscopy or augmented fluoroscopy).

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Another system uses real-time endobronchial augmented fluoroscopic navigation (BodyVision Medical LtD., Israel). This system enables lesion tracking during breathing movement and may improve lesion localization and diagnostic yield. (16)

Others report that VBN-guided (Olympus Medical Systems, Tokyo, Japan) rEBUS-transbronchial diagnosis without fluoroscopy has equivalent diagnostic yield to fluoroscopy in nodules with a bronchus sign.(17) Comparative evaluation of these techniques is required.

Transparenchymal Nodule access (TPNA)

rEBUS, VBN, ultrathin scopes and ENB improves diagnostic yield of pulmonary nodules compared to standard bronchoscopy; however, diagnostic yield still depends on lesion size, lesion location and presence of a bronchus sign.

Some nodules lack a bronchus sign and are so distant from a bronchus that bronchoscopic sampling techniques fail. For these situations, Transparenchymal Nodule Access (TPNA) was developed. The Archimedes Virtual Bronchoscopy Navigation System (Broncus Medical, Mountain View, Calif., USA) reconstructs HRCT data into a 3D model to provide virtual guidance of sheath placement through an airway wall and lung parenchyma into a lesion. (18, 19)

A sheath with radiopaque marker bands is used to tunnel through lung parenchyma to the nodule, samples are taken real-time under fused fluoroscopic guidance (Figure 3, Panel A).

Herth (20) presented a dataset at the ERS conference showing that the yield of TPNA depends on lesion size.

The transbronchial access tool (TBAT; CrossCountry™ TBAT, Medtronic, Minneapolis, MN) biopsies peripheral lung nodules using rEBUS or ENB or rEBUS + ENB to diagnose peripheral lung nodules. (Figure 3, Panel B). TBAT with rEBUS and ENB plus cone beam CT may

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increase diagnostic yield close to 100%.(21-23) Procedural time and radiation exposure is higher with use of CT. More data is needed to confirm the success of this technique.

Imaging and Navigation

CT Bronchoscopy

Computed tomography (CT)-guided biopsy helps the bronchoscopist biopsy fluoroscopically invisible lesions. Ultrathin bronchoscopy with CT guidance has 79% and 80% diagnostic sensitivities when a bronchus or artery is at the center of the lesion, respectively.(24) Combining VBN with CT-guided biopsy using an ultrathin bronchoscope may be helpful, especially LUL lesions .(25) (24) Others failed to increase diagnostic yield with CT guidance suggesting that technical expertise may be crucial. (26) Lesion location (superior segment of lower lobes), more distal navigation, and a CT bronchus or artery sign affects diagnostic yields. (24) Cone beam CT (CBCT) imaging to diagnose lung lesions is a modification of techniques used in digital angiography.(27-29) With this technique, CBCT images are obtained and the target is overlaid on fluoroscopic images. Real-time multiplanar confirmation of lesion location in relationship to biopsy tools addresses CT-to-body divergence. A drawback is radiation bursts used to procure images during CBCT “spins. One report using CBCT with real-time ENB with or without rEBUS reported navigational and diagnostic yields of 91% and 70%, respectively.(28) In malignant cases, diagnostic yield was 82% for lesions within 25 $\pm$ 18mm of the pleura. (28) A study using CBCT with augmented fluoroscopy (Philips Allura Xper FD20 system with Oncosuite); PhilipsHealth, UK) plus ENB reported a diagnostic yield of 83.7%; there was no relationship between diagnostic yield and lesion size, location, fluoroscopic visibility or bronchus sign. (30) CBCT with ENB and hook-wire localization enhances diagnosis and resection of lung lesions during the same session. (27) Further investigation should compare CBCT diagnostic yield vs. less costly modalities with lower radiation exposures.

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Adjunctive bronchoscopic local imaging techniques

Lung cancer screening has precipitated a shift from central to more peripheral nodules for lung cancer evaluation. This has prompted development of new techniques based on sound optical, biochemical and physiological principles to provide greater in vivo guidance while biopsying small lung lesions. The clinical value of these techniques are currently unknown but have potential to help diagnose peripheral lung cancers.

Optical coherence tomography (OCT)

OCT uses near infrared light to create high-resolution images at a 'histology' level with 10-15μm resolution and 2-3mm depth. (31) It can identify and quantify changes in airway walls (32, 33), histologically examine lung parenchyma(34-36), and examine nodules and pulmonary vasculature. Images are captured using a 1mm probe via the bronchoscope. OCT's clinical applications include identifying bronchial lesions, (37-39) airway remodeling,(40-43) subtyping interstitial lung diseases (ILD)(44),and assessing vascular lesions due to pulmonary arterial hypertension (45, 46) or thromboembolic disease.(47)

OCT has been used with other modalities to enhance diagnostic yield. Autofluorescence bronchoscopy–guided OCT imaging provides *in vivo* imaging of preneoplastic bronchial lesions to study their natural history and the effects of chemopreventive intervention. In high-risk heavy smokers, Lam reported that dysplasia and carcinoma *in situ* (CIS) can be distinguished from lower-grade lesions.(37) Polarization-sensitive OCT (PS-OCT) is another OCT imaging modality that is endoscope- and/or needle-compatible. It provides large volumetric views of lung tissue microstructure at high resolution (e.g.,10 mm) while simultaneously measuring birefringence of organized tissues like collagen or airway smooth muscle. In 64 lung nodule samples, PS-OCT accurately classified tumor regions with higher (>20%) from lower fibrosis thus yielding higher tumor content with PS-OCT directed biopsy.(48)

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Confocal laser endomicroscopy (CLE)

CLE uses low power laser bundles to create real-time microscopic images at a “cellular” level. CLE has a resolution up to 3.5μm, with a 240μm maximum depth and 600μm field of view.(47) Contrast can enhance visualization of different cellular/tissue components. Images are captured using a probe-based CLE via bronchoscope or 19-gauge needle. It may help detect lung cancer, (49-51)ILD(52, 53), lung allograft rejection (54)and mediastinal lymph node pathology.(55)

Image enhancement

Autofluorescence bronchoscopy (AFB) utilizes green and red spectrum light to detect mucosal alterations. Normal mucosa presents green color, while precancerous and cancerous lesions absorb the green spectrum and turn magenta. Narrow band imaging (NBI) removes all wavelengths except two that are absorbed by hemoglobin thereby creating contrast between the vasculature (Cyan) and surrounding mucosa (Brown). AFB(56)and NBI (57-60)are superior to white light bronchoscopy in detecting dysplasia, CIS or invasive carcinoma.(61) Image enhancement has struggled for a role in bronchoscopy because no well-defined population exists for general use,(62) poor standardization of pathological dysplastic criteria and weak evidence for treatment of CIS.(63) It may be useful in patients with abnormal sputum cytology or previous dysplasia to delineate tumor margins.(64)

Thin convex probe endobronchial ultrasound (Thin-EBUS)

Convex probe endobronchial ultrasound is designed for mediastinal and hilar lymph node staging and has limited size and flexibility to direct biopsy of lung lesions except those centrally located. Development of a Thin-EBUS scope that has smaller size and greater flexibility may improve smaller airway access.(65) In ex-vivo human lungs, it provides superior access to

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segmental and subsegmental bronchi.(66) Thin-EBUS could provide better access to interlobar lymph nodes and peripheral lung lesions.

Technological changes in the Bronchoscope

Ultrathin bronchoscopy

The small size of the peripheral airways limits the ability of conventional bronchoscopes to navigate to peripheral lesions. The working channel of conventional pediatric bronchoscopes limits the size of tools needed to diagnose peripheral nodules. (67) Development of ultrathin bronchoscopes (~2.8 -3.5 mm outer diameter) allows for greater maneuverability to traverse small airways. Although no strict definition of ultrathin exists; most have outer dimensions $\leq$ 3.2 mm. A retrospective analysis of 209 malignant lesions biopsied with an ultrathin bronchoscope reported diagnostic yields of 63% in lesions $\leq$ 2 cm. (68)A metanalysis of ultrathin bronchoscopy reported an overall diagnostic yield of 70% when combined with other modalities (e.g., VBN, rEBUS and fluoroscopy). (69) A concern is that working channel size limits the size of collected specimens. A multicentered trial reported that ultrathin bronchoscopy was superior to thin bronchoscopy to diagnose peripheral lung nodules $\leq$ 30 mm. (68). The ultrathin bronchoscope reached more distal bronchi (median fifth vs. fourth generation bronchi). Diagnosis of benign disorders was lower than malignant lesions despite using the ultrathin bronchoscope.(70) The type of image guidance (fluoroscopy vs VBN vs CT) used with the ultrathin bronchoscope and sampled lobe impacts diagnostic yields.(24, 25, 71)

Robotic bronchoscopy

Robotic-assisted bronchoscope systems can navigate to small peripheral airways under continuous visualization while maintaining a static curved position. This advantage keeps biopsy tools and even ablation devices locked on the targeted lesion despite flexed articulation. (72-74)

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Initial experience has been reported in 15 patients.(73) Biopsy samples were taken from 93% of subjects with lesions 2.6 mm in diameter; closest edge was 0.6 mm from the pleura. Cancer was confirmed in 60% of lesions; time to biopsy was 45 minutes in the first five cases and 20 minutes in the last nine. Another robotic device (Ion Endoluminal System (www.intuitive.com/ion) received FDA clearance in August 2019. (https://www.therobotreport.com/ion-lung-biopsy-intuitive-surgical-fda/) It has Fiber Optic RealShape (FORS) technology with ultra-thin and maneuverable catheters that navigate to the lung peripheral with maintenance of catheter stability. Fielding studied 29 subjects with mean lesion size of 12.2 ± 4.2 mm; 41.4% had absent CT bronchus sign. In 96.6% of cases, target was reached and samples were obtained.(75) An overall diagnostic yield of 79.3% was reported with 88% yield for malignancy.

Malignant Solitary Pulmonary Nodule: Therapeutic Approaches

Solitary pulmonary nodule

Guidelines recommend surgical resection of early stage non-small cell lung cancer (NSCLC) (76),but many patients are unsuitable (77). The only non-surgical non-pharmacological option is stereotaxic body radiation therapy (SBRT), which is highly effective but not without complications.(78) The need exists for other non-pharmacological options that are similarly effective, but with less complications.

Advances in navigational bronchoscopy enable accessing a lung tumor and treating it. Various bronchoscopic ablation technologies might be possible: radiofrequency ablation (RFA), microwave ablation (MWA), photodynamic therapy (PDT), brachytherapy, cryoablation, vapor thermal ablation or direct therapeutic injection. Most technologies are still in preclinical stages or undergoing small feasibility trials.

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Radiofrequency Ablation (RFA)

RFA uses high frequency alternating current to deliver thermal injury with an electrode inserted into the tumor. RFA generates a tissue destruction zone around the electrode tip; treatment zone and tumor death may be affected by surrounding tissue. Damage to aerated lung surrounding tumor is minimized by air's insulating effect. (79, 80) Koizumi (81) reported a local control rate of 83 % using endoscopic RFA; median progression-free survival was 35 months and overall 5-year survival was 61.5%.

Microwave Ablation (MWA)

Microwave ablation is a heat-based therapy that generates an elliptical-shaped electromagnetic field with microwave frequency ranges between 300 MHz to 300 GHz via a probe inserted into the lesion. Like RFA, microwave ablation induces coagulation necrosis by heating target tissue to temperatures > 60°Celsius. An endoscopically directed flexible gas-cooled microwave antenna has been tested in a porcine model (82). Clinical trials with endoscopically delivered MWA are ongoing. (ClinicalTrials.gov Identifiers: NCT03569111; NCT04005157 and NCT03769129).

Cryoablation

Cryoablation causes cell death using alternating freeze and thaw cycles. The exact lethal temperature threshold is unclear; some experiments suggest -20°C as a minimum threshold. Yamauchi reported mean local tumor progression-free interval was 69 months and median survival was 62 months using percutaneous cryoablation in 22 inoperable NSCLC patients (83) Zheng (84) recently reported animal data using a flexible probe; human data is unavailable.

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Bronchial Thermal Vapor Ablation (BTVA)

BTVA has been used in bronchoscopic lung volume reduction and may have potential to treat focal cancers. An advantage of water vapor is rapid energy delivery. A porcine model demonstrated that uniform necrosis can be bronchoscopically delivered to a focal lung region (85). A first-in-human trial has begun. (ClinicalTrials.gov Identifier: NCT03198468)

Brachytherapy (HDRT)

HDRT is used to palliate malignant central airway obstructions. Experience for peripheral brachytherapy is limited; only small case series are published (86, 87). Most have used 5 Gy administered 3 times per week. The requirements for repeated applications and placement of a guide sheath are limitations.

Photodynamic Therapy (PDT)

PDT has been used for malignant central airway obstructions and carcinomas-in-situ. After administration of a photosensitizing agent with selective uptake by tumor cells, the photosensitizer is activated endoscopically by a specific laser light. The photosensitizer produces highly reactive oxygen species that cause cell death. Chen (88) treated 3 patients with local control at 1-year. A newly developed parallel-type ultrasmall composite optical fiberscope (Laser-eYe Ultrathin fiberscope [LYU]) couples simultaneous imaging and phototherapy and was effective in preclinical lung cancer models.(89) This new laser device has potential to treat peripheral lung cancers.

Central airway obstruction (CAO)

CAO is symptomatic obstruction of the trachea, mainstem bronchi, bronchus intermedius or lobar bronchi.(90, 91) Tracheal obstruction causes exertional symptoms when tracheal diameter

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is 8mm or ~ 30% cross-sectional area, rest symptoms develop < 5mm or <20% cross-sectional area. (92-94)

CAO can be divided into malignant or non-malignant causes. Malignant disease is usually related to locally advanced thoracic malignancies. At presentation approximately 10% of lung cancers have evidence of CAO.(95) Tracheal invasion constitutes a T4 malignancy in the 8th TNM classification,(96) tracheal invasion without metastasis constitutes stage 3A disease with a median survival of 29.3 months, nearly double compared to prior years.(97) Primary tracheal tumors are rare; in adults these are mostly malignant and due to squamous cell carcinoma, adenoid cystic carcinoma or carcinoid.(98) Primary tracheal tumors should be treated with resection for most patients with benign lesions, tumors of intermediate aggressiveness, and localized malignant tumors.(99)

Non-malignant disease includes post-intubation, (100, 101)post-tracheostomy,(93) infection related;(102) transplant airway disease (102)and autoimmune conditions.

CT imaging is essential to evaluate CAO, it provides insight into etiology, extent, morphology and vascular involvement. (103-106) 3D reconstructions with vascular and mediastinal anatomy assists with case planning and stent preparation.

Flexible bronchoscopy evaluates morphology and extent of CAO and can provide diagnostic specimens. (107)Manipulation of CAO with a flexible can be dangerous; even minimal manipulation can cause edema or hemorrhage that precipitates airway compromise. Therapeutic instruments (laser, APC, stent deployment) can be used with a flexible bronchoscope.(108) Endobronchial ultrasound assesses invasion depth and vascular structures during therapeutic bronchoscopy. (109)

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Rigid bronchoscopy is the gold standard for CAO management .(90, 110) It allows airway manipulation with the ability to ventilate, suction and tamponade bleeding while debulking tumor.(107) Its' large working channel allows removal of large tumors and deployment of silicone stents, but can also cause airway damage. A flexible bronchoscope can be inserted via the rigid bronchoscope to enhance maneuverability.

After appropriate patient selection(111, 112) therapeutic bronchoscopy for CAO can be performed with acceptable complications and mortality. (113, 114) Therapeutic bronchoscopy improves quality of life, (114-116), lung function(117) weans patients from ventilation (118), stabilizes patients before definitive therapy, (119) and improves survival similar to comparable cancer stage patients without CAO.(120, 121)

Central airway obstruction (CAO): Treatment

Therapeutic destruction

Therapy for malignant CAO includes mechanical debridement with forceps, cutting tools or mass coring with a rigid bronchoscope. (107) Thermal therapies with laser, APC and electrocautery can provide immediate relief. Depending on the laser and its settings, it can be a cutting tool, or can coagulate and vaporize the tumor. There is a low rate of laser related complications; but hemorrhage, airway fire, and fistula have been reported.(122-125) APC is not ideal for large tumors but helps with mechanical debulking by coagulating the tumor and controlling bleeding. (126) Electrocautery can be used but requires tissue debulking.(127) Thermal therapies require reduced oxygen environments which limits use in hypoxemic patients.

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Photodynamic therapy (PDT)

Photodynamic therapy (PDT) is indicated for non-operable malignant CAO. (128) The effect is delayed and requires repeat bronchoscopy for airway clearance. Adverse reactions include photosensitive skin rash and hemoptysis.(129)

Cryotherapy

Cryotherapy can be used as a spray (130) or a probe (131) for malignant and non-malignant CAO. The cryoprobe requires removal from the airway between biopsies; serious hemorrhage has been reported.

Microdebrider

A microdebrider is a hollow suction tube with an internal rotary blade; the tissue is macerated by the blade and simultaneously removed by suction. This allows field visualization and rapid debridement without perforation. (132, 133)

Airway dilation

Airway dilation uses high pressure catheter balloons, bougie devices or a rigid bronchoscope. (134) Dilation is combined with other therapies; radial incisions for focal stenosis to prevent mucosal tear(135), debridement of tissue, and stent placement.(136-138) Sustained airway patency after balloon dilation is variable(139, 140); the procedure usually needs repeating, surgery, or stenting for recalcitrant disease.(141) Attempts to sustain benefit with drug eluting balloons has been reported.(142)

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Chemo injection

Direct injection of chemotherapeutic agents into CAO has been reported to be feasible. (143-145)

Stents

When selecting a stent to manage CAO, one must consider the disease process, radial force required, duration of use and insertion technique. The ideal stent should be: (1) easy to insert and remove, yet not migrate; (2) of sufficient strength to support the airway but flexible enough to promote secretion clearance; (3) biologically inert to minimize granulation tissue; and (4) available in multiple sizes. (90)

Silicone stents developed (146)are inserted via a rigid bronchoscope, they are inexpensive, easy to modify, and remove. The major issues are mucostasis (147) and migration. Silicone stents have reduced granulation tissue reaction,(148) the silicone Y stent is ideal for lesions at the carina or dynamic collapse of the distal trachea and mainstem bronchi. (91)

Self-expandable metal stents (SEMS) are the most commonly used stents. SEMS conform to the airway and have favorable internal to external diameters that aids mucus clearance. Indications include recurrent stenosis; malignant airway obstruction(9, 149-151) and transplant airway stenosis. (152-154)They are used in expiratory central airway collapse to predict response to tracheoplasty. (155)

Balloon-expandable metal stents are malleable, they can be bent and perforated to aerate collateral bronchi. Currently, their limited diameters make them most useful in lobar airways.(156, 157)

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Benign CAO patients' survive longer than malignant patients and thus experience more complications. (150) Attempts to circumvent these issues have led to stents made with biodegradable polymers.(158) Use of these stents is limited to reports in pediatric patients and transplant airway disease. (159-163)A pilot study in adults with transplant airway complications reported biodegradable stents to be effective but required repeated procedures(161) (158)

The tracheobronchial tree is well suited to 3D printing using multidetector CT data. 3D models have been used for procedure planning, stent design and assessment of flow limitation.(164-169)

Agents may be applied to stents that could retard bacterial colonization, granulation tissue formation or malignant growth. (29)

Mediastinal Lymph Node Staging

Real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for lung cancer staging was introduced in 2003. (170) Since then, EBUS-TBNA has become essential for minimally invasive sampling of mediastinal lymph nodes for non-small cell lung cancer (NSCLC).(171) (172)

EBUS-TBNA is the initial modality for lung cancer staging for multiple reasons. The first is less than ideal assessment by staging modalities such as positron emission tomography-computed tomography (PET-CT). Next is its excellent safety profile. Complication rates from multiple databases reports EBUS associated complication rates at ~ 1%. Most complications are minor (cough, bleeding at puncture site) but more serious complications (pneumothorax, mediastinitis, pericarditis and death) have been reported.(173) The diagnostic accuracy of EBUS-TBNA is similar to mediastinoscopy.(171-174) Compared to mediastinoscopy alone, when EBUS-TBNA and mediastinoscopy are used in conjunction, the sensitivity for detection of mediastinal

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metastasis improves from 79% to 94%.(175) Follow-up data revealed similar 5yr survivals between endoscopic and surgical staged groups. (176)

Standard practices for EBUS-TBNA staging involves evaluation and sampling of N3 nodal stations, followed by N2 and N1 stations. Sampling all lymph nodes > 5mm in short axis is optimal to maximize procedure sensitivity.(177) Stations traditionally accessible by EBUS-TBNA include 2R/2L, 4R/4L, 7, 10R/10L and 11R/11L. Stations 5 and 6 are inaccessible by EBUS-TBNA, unless a transvascular approach is employed. In place of bronchoscopic ultrasound, transesophageal and gastric use of the EBUS scope (EUS-B), can be performed. EUS-B allows more complete staging of lung cancer patients including stations 8 and 9, and alternative access to stations 2L and 4L. (178) EBUS can evaluate airway tumor infiltration better than CT imaging.(179)

Technical aspects of EBUS-TBNA may maximize procedural yield. Aspiration needles come in 19g, 21g, 22g, and 25g sizes. Trials comparing 21g to 22g, as well as use of a 19g needle show improved sample volume with larger needle size, but larger needle size has not been shown to correlate with diagnostic yield.(180, 181) Larger needles may be considered if lymphoma or sarcoidosis is suspected. Use of mini-forceps via EBUS may increase sample volume.(182)

In the NSCLC era of tumor molecular analysis, sample adequacy is important in lung cancer staging. During node sampling, diagnostic yield plateaus after three passes.(183) Rapid on-site evaluation (ROSE) ensures adequate sampling and reduces needle passes.(184) EBUS-TBNA sampling is adequate for generation molecular analysis including ALK, EGFR mutations and PDL1 expression.(185, 186)

Ultrasound characteristics of lymph nodes provide insight into underlying pathology. Independent predictors of metastasis included rounded shape, distinct margins, heterogeneous

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echogenicity, and coagulation necrosis.(187) An aggregate scoring system that uses the presence of matting, non-hilar vascular pattern perfusion, absence of central hilar structure, and rounded shape had a sensitivity of 93%, specificity of 55%, positive predictive value of 73%, and negative predictive value of 82% to predict malignancy if at least two factors were present.(188)

Elastography

Elastography has been used in breast, thyroid, and hepatic diseases to measure elastic properties. It has also been used to evaluate mediastinal lymph nodes. The color map used with elastography includes red, yellow, green and blue corresponding respectively from least to most stiff. Elastogram colormetric patterns comprise three groups: Type 1 homogeneous green (predominantly green with yellow and red areas), Type 2 mixed (predominantly green with focal blue areas), or Type 3 homogeneous blue (predominantly blue). (Figure 4)

Current data suggests that EBUS-Elastography is safe and may provide predictive information regarding malignant lymph node infiltration. Whether EBUS-Elastography precludes TBNA of lymph nodes is uncertain. A study using similar classification types found a sensitivity of 87%, specificity of 68%, positive predictive value of 80%, and negative predictive value of 77% when type 1 was considered benign, and type 3 malignant.(189)

Obstructive lung diseases: Interventional bronchoscopic treatment

Asthma

Despite a multiple inhaled therapies, patients with asthma may remain symptomatic and require chronic oral steroids or expensive biologics. Consequently, a need exists for other therapeutic options.

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Bronchial Thermoplasty

Bronchial thermoplasty is an effective bronchoscopic treatment for asthma. Smooth muscle hypertrophy is key in severe asthma and its reduction may alleviate symptoms and down-regulate airway inflammation. Bronchial thermoplasty is a catheter-based therapy that utilizes radio-frequency energy to heat the airways. A thermocouple within the catheter detects temperature and algorithms within the generator allows smooth muscle temperature to reach 65^{o}C to induce permanent smooth muscle ablation. (190) The mechanism of action was demonstrated by short- and long-term canine studies and has been confirmed in humans. (191-195)

Clinical Evidence

Two cohort and two randomized controlled trials have reported that bronchial thermoplasty is safe and effective in patients with mild to severe asthma. A study in mild to moderate asthma patients demonstrated reductions in symptoms and reduced bronchial hyper-responsiveness. (196)A subsequent study in moderately severe patients (AIR Trial) confirmed improvements in quality of life and symptom scores, but no change in pulmonary function. (197)An uncontrolled study in 30 patients with severe disease (RISA Study) reported benefits in asthma symptom scores and quality of life. (198) A 50% reduction in steroid dose has been reported following bronchial thermoplasty in steroid dependent patients. (198).

A sham-controlled study was performed in symptomatic patients with moderate to severe asthma on high dose inhaled steroids. (199) After bronchial thermoplasty there were significant improvements in asthma quality of life questionnaire measures (AQLQ) and reduced exacerbations, healthcare utilization and days lost from work or education. Reductions in exacerbations and hospitalizations were maintained long term.(200)

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Real Life Treatment Experience

The US study (PAS2 Study, Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma) collected registry data and demonstrated similar benefits to AIR2. (201)There was a 44% reduction in severe asthma exacerbations and 55% decrease in emergency room attendance following bronchial thermoplasty.

Future Endoscopic Options

Historical studies suggest a role of the parasympathetic nervous system in hypersensitivity and benefit with denervation. Targeted lung denervation has been studied in COPD but may also have a therapeutic role in severe persistent asthma.

Bronchoscopic Treatment of Emphysema

Multiple interventional possibilities, both surgical and bronchscopic, exist for patients with advanced emphysema based on clinical, physiological, and radiological assessment. Figure 5 provides an overview of treatments based on clinical assessment.

Endoscopic Valve Placement

In patients with severe emphysema, destruction of the lung leads to both a reduction of gas exchange surface and static and dynamic hyperinflation. Therapeutic strategies aim to reduce air-trapping in order to improve respiratory mechanics, physical activity and even symptoms(202, 203).

Endoscopic valve placement via a flexible bronchoscope is a minimally invasive technique that mimics the benefits of lung volume reduction surgery (LVRS). Two types of one-way valves are commercially available: IBV (Spiration, Olympus, Tokyo, Japan) and EBV (Zephyr, Pulmonx, Inc., Neuchatel, Switzerland), they have different shapes but similar function. Both block inspired air

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entry into the treated lobe while air and secretions escape during expiration. Although IBV was originally used for bilateral treatment with incomplete occlusion (204, 205), unilateral lobar occlusion of the most diseased lobe is the preferred technique for either valve(206).(Figure 6)

Valve treatment is suggested only in patients without collateral ventilation (CV)(207). Absent or low CV is presumed in cases with complete fissures on computed tomography (CT). However, CV can also be measured endoscopically with the Chartis system (Pulmonx, Inc., Neuchatel, Switzerland)(208). Using these criteria, RCTs show clinically meaningful improvements in pulmonary function testing, 6-MWD and quality of life (QoL). Mean changes in $FEV_1 \geq$ than +20% and an increase of 33m to 79m in 6-MWD were reported. Although interindividual variability in response is high, 60% of treated patients achieve minimal clinically important difference (MCID) in outcomes(209-211).

In approximately 20-30% of treated patients a postinterventional pneumothorax is expected; it most frequently occurs in the first three days and can be life-threatening. Pneumothorax usually requires chest tube placement, valve removal and rarely surgical intervention (212).

Patients who develop complete atelectasis after valve placement show improvements in lung function, exercise capacity, QoL and survival(213)

Lung volume reduction coil treatment (LVRC)

LVRC (PneumRx/BTG, CA, USA) is a bronchoscopic treatment for emphysema patients with severe hyperinflation (Residual Volume (RV)>200% of predicted), absence of significant airway pathology,(214) who are not candidates for EBV or LVRS (215). The LVRC is a shape-memory nitinol implant (Figure 7) of which 10 to 14 are fluoroscopically placed in the most diseased lobe of each lung during sequential bronchoscopic procedures.(216) LVRC reduces static hyperinflation by improving airway resistance, and from secondary inflammation due to

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mechanical tissue stress.(217-220) Initial trials showed improved pulmonary function, quality of life and exercise performance.(219, 221-224) A larger randomized controlled trial failed to reproduce earlier trial results, but still showed improved lung function and quality of life.(217) The benefits of LVRC treatment persist for up to three years,(224) and can potentially be repeated, however, the benefit is not as robust as initial treatment.(225) A U.S. Food and Drug Administration (FDA) panel concluded that LVRC benefits did not outweigh risks and it was denied clinical approval.(226) A sub analysis of RENEW suggests that patients with a RV > 200%, absence of airways disease and coil placement in the lobe with most emphysema had better outcomes.(214) These parameters are used for entry criteria in an ongoing trial.(227).

Thermal Vapor Ablation / Polymeric Lung Volume Reduction

Bronchoscopic Thermal Vapor Ablation (BTVA) and Polymeric Lung Volume Reduction (PLVR) target hyperinflation in symptomatic emphysema patients despite optimal pharmacological treatment. Both techniques incite inflammatory reactions to induce reduction of emphysematous areas. BTVA and PLVR treatments have some advantages over EBV, their efficacy does not depend on collateral ventilation and treatment occurs on a segmental not lobar level. Segmental treatment is important since many patients have intralobar heterogeneity.(228) The disadvantage of BTVA and PLVR is their irreversibility.

During BTVA, segmental application of 100°C heated water vapor promotes inflammation to induce volume reduction of emphysematous segments.(229) A RCT confirmed the efficacy of BTVA in 46 patients with upper lobe predominant emphysema.(230) At 6 months following bilateral treatment, significant improvements in FEV_1 and SGRQ occurred. BTVA is being evaluated for patients with homogeneous emphysema. (ClinicalTrials.gov Identifier: NCT03670121)

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PLVR deploys a synthetic polymer into emphysematous lung segments to induce inflammation and resultant volume reduction. A RCT evaluated the safety and efficacy of PLVR in 34 patients with upper lobe predominant emphysema and showed significant improvement in lung function.(231) However, the procedure had a high rate of adverse events. The results of another multicenter RCT are pending. (ClinicalTrials.gov Identifier: NCT00884962)

Since both techniques induce inflammatory reactions, their most common adverse events are COPD exacerbations, and pneumonitis/pneumonia. BTVA has limited clinical availability and PLVR is currently under clinical trial investigation.

Targeted Lung Denervation

Reflex signaling via pulmonary branches of the vagus nerve is involved in the pathophysiology of COPD (232). Airway submucosal glands are innervated by pulmonary ganglion (233) and stimulation of parasympathetic efferent or sensory afferent (C fibers and stretch receptors) fibers initiate direct (efferent) (234) or reflex (afferent) (235, 236) mucus hypersecretion. Vagal nerve signaling facilitates disease-related airway hyperresponsiveness, and vagotomy abolishes the effect (237, 238). Cholingergic hyperactivity in COPD causes airways hyperresponsiveness, airflow limitation, gas trapping, mucus hypersecretion, and exacerbations. Blocking parasympathetic efferent lung signaling may complement bronchodilator therapies for COPD.

Targeted Lung Denervation (TLD) targets parasympathetic branches of the vagus nerve that run alongside the mainstem bronchi (Figure 8). TLD directs radiofrequency energy to pulmonary branches of the vagus nerve to disrupt signaling to and from the lung. TLD uses dual-cooled technology to protect the airway epithelial surface while delivering heat to a targeted depth where pulmonary vagus nerve branches reside. A preclinical study demonstrated that TLD disrupts vagal fibers histologically and produces physiologic changes associated with sensory/motor reflex signaling (239).

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The first-in-man clinical study of TLD,IPS-I, demonstrated that TLD provides a bronchodilator effect similar to anticholinergic therapy with a dose (power) dependency effect (240). TLD with an inhaled anticholinergic produced greater bronchodilator effect than either therapy alone (241). IPS-II demonstrated the feasibility and safety of a single whole lung TLD procedure (242).

AIRFLOW 1 confirmed safety and feasibility with a flexible bronchoscope, reduced gastrointestinal side effects associated with ablation near the esophagus, and the safety of TLD using a 32W dose. (243) AIRFLOW 2 demonstrated that TLD treatment produced less airway related adverse events and fewer COPD hospitalizations (ClinicalTrials.gov Identifier: NCT02058459). An international multicenter randomized sham controlled TLD trial is evaluating if TLD reduces COPD exacerbations. (ClinicalTrials.gov Identifier: NCT03639051)

Chronic bronchitis

Chronic bronchitis patients have a poor quality of life, increased hospitalizations, greater lung function decline and increased mortality. It is characterized by excessive mucus hypersecretion by goblet cells predominantly located in the large airways. Treatments include smoking cessation, mucolytics, macrolides, anticholinergic agents, PDE-4 inhibitors, glucocorticoids, and chest physiotherapy; but are limited in treating symptoms or halting disease progression. (244, 245)

Bronchial Rheoplasty

Bronchial rheoplasty (RheOx System™ (Gala Therapeutics, Menlo Park, CA) delivers non-thermal energy to ablate airway mucosal cells and reduce goblet cell hyperplasia. The RheOx catheter is inserted via a bronchoscope from the subsegmental airways to the main carina while energy is delivered during electrode expansion (Figure 9).

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In a multi-center feasibility study 25 patients with symptomatic chronic bronchitis underwent rheoplasty; procedure success was 100%. (13). Two patients experienced serious device-related adverse event (pleural effusion and mucosal scarring); four patients had 7 COPD hospitalizations. Most adverse events occurred within 30 days of bronchoscopy. Significant improvements in SGRQ and CAT scores were observed at 6- and 12-months. A reduction in goblet cell hyperplasia was observed. A U.S. clinical study is underway. (ClinicalTrials.gov Identifier: NCT03631472)

Liquid Nitrogen Metered Cryospray

The Rejuvenair Liquid Nitrogen Metered Cryospray™ (CSA Medical, MA, USA) is another potential bronchoscopic treatment for chronic bronchitis (Figure 10). It ablates diseased airway epithelial using liquid nitrogen at -196°C, thereby inducing a non-scarring, non-inflammatory healing process.(246) The system delivers pre-determined quantities of liquid nitrogen depending on anatomic site and gender and is locally controlled by thermocouple feedback. Treatment is performed in two sequential bronchoscopic procedures of approximately 45 minutes with intermittent airway circuit interruption to permit nitrogen gas egress. The Rejuvenair system was first tested in humans with sprays delivered into a resected lobe to demonstrate feasibility and safety.(247) It's use for treatment of chronic bronchitis is under investigation (Rejuvenair® study - ClinicalTrials.gov Identifier: NCT02483637).

Parenchymal lung diseases: Diagnosis

Diagnosis of diffuse parenchymal lung diseases (DPLD) relies on multidisciplinary evaluation.(248) Histologic data contributes to the diagnosis.(249-251) Surgical lung biopsies, the historical gold standard, are performed annually in $\geq$ 10,000 U.S. patients and provides samples of size and quality generally sufficient for a diagnosis. However surgery has increased risks; in-hospital mortality is 1.7% and 16% for elective and non-elective procedures,

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respectively.(252) Accordingly, less invasive alternatives are needed. Transbronchial forceps biopsies have a diagnostic yield of ~ 20% in DPLD.(253-255)

Transbronchial cryobiopsies have been proposed as a possible option. They are performed via either flexible or rigid bronchoscopy, using a cryoprobe advanced under fluoroscopy to the lung periphery, approximately 1 cm from the pleura. The probe is activated, releasing compressed gas (carbon dioxide or nitrous oxide) to the probe tip which instantly freezes lung tissue that is extracted, en-bloc with the bronchoscope.(256) Biopsies typically measure 5 mm, are devoid of crush artifact, and have superior histopathologic quality to forceps biopsies. There are, however, major downsides. Biopsy size precludes extraction through the working channel of the flexible bronchoscope: both must be removed together which exposes the patient to potentially severe endobronchial bleeding without maintaining a wedged position. Clinically significant bleeding occurs in 40% of patients. Cryobiopsies obtained at the lung periphery cause pneumothorax in 12%.(257) Mortality after cryobiopsy remains substantial, estimated around 0.3%.(139)

Cryobiopsy techniques vary considerably and the role of cryobiopsy remains controversial.(258) Besides procedural risks, critics highlight a lower diagnostic yield of cryobiopsies compared to surgical lung biopsies, estimated at 80% and 95%, respectively, and the lack of direct comparisons.(139) Proponents of the procedure offer counter arguments: 1) cryobiopsy and surgical lung biopsy offer comparable data to a multidisciplinary team (259), and 2) head-to-head comparisons only address histologic sample quality which needs to be balanced with the risks inherent to intervention. In that regard, cryobiopsies remain a promising alternative to the status quo. Detailed recommendations on effective and safe cryobiopsy practice provide guidance on patient selection, the need for multidisciplinary discussion, use of an endobronchial blocker to mitigate bleeding, and the need for proper training and expertise.(259)

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Certification Training issues

The time-honored apprenticeship model of “see one, learn one, teach one” is not acceptable. Its flaws include training on real patients in high-stress environments, inadequate preparation for uncommon events, and the absence of systemic and structured feedback. (260)

For the cognitive component of procedural training, traditional tools such as books and lectures should be supplemented with newer approaches like interactive on-line learning and case-based discussion. Teaching should address all procedural aspects including patient selection, pre-procedural, procedural, and post procedural care and communication of results to patients and the care team. It’s critical to educate proceduralists on when and how to decline a procedural request and the education of referring health care providers. (261)

Simulation is an effective tool for teaching bronchoscopy skills and available in two forms: low and high fidelity. (262, 263) Low fidelity simulation consists of molded models that offer realistic airway-like structure or silicone-based lymph nodes so learners can master anatomy and practice various sampling techniques. High fidelity simulation consists of computer-generated three-dimensional models of the airways, lymph nodes and vessels with various iterations of anatomy, clinical situations and even complications. High-fidelity simulation facilitates acquisition of bronchoscopy skills.(262, 264) Simulation models are available for basic bronchoscopy and EBUS skills. Explanted animals’ lungs or cadavers are effective in training for higher-risk procedures (e.g., cryobiopsy, ablation therapy or stent placement).

Measuring competency in procedural performance is critical to assure best outcomes. Earlier guidelines published focused on procedural volume to determine competency.(110, 265) However, this approach is less favorable since learners acquire skills at different volume thresholds.

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Newer guidelines emphasize the need to move to skill acquisition and knowledge-based assessments.(266) Checklist-based assessment tools aid assessment of the learner performing the procedure and scores procedural steps based on objective criteria. These tools are validated and reliable in discriminating skill levels.

Optimal training in interventional bronchosopic procedures should incorporate traditional models (lecture, books) and newer approaches including digital media platforms, case-based interaction and simulation.

Interventional bronchoscopy: The future

In the near future, new approaches for many different lung diseases should become available: biodegradable stents, 2nd and 3rd generation endobronchial valves, better nonpharmacological treatments for chronic bronchitis and airflow obstruction, and new treatments in patients with emphysema who exhibit collateral ventilation (267). Ablative procedures for early cancerous lesions will advance and clinical trials will determine their effectiveness.

In order to access small peripheral lesions precisely, navigational methods need further development. The advantages and disadvantages of ultrathin bronchoscopy, thin bronchoscopy with guided sheath catheters and robotic assisted bronchoscopy requires comparative studies of diagnostic yields and cost effectiveness.(73, 75) Imaging support during the procedures must be improved. Smaller EBUS bronchoscopes and rEBUS tipped biopsy catheters should be compared to cone-beam-CT and augmented fluoroscopy in their abilities to provide real-time confirmation of lesion access during diagnostic and treatment interventions (268). This is especially true for semi-solid lesions where rEBUS currently has limitations.

The importance of training clinicians to be well versed in bronchial and lung anatomy who perform bronchoscopy is paramount and must be coupled with the skills need to navigate the

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bronchoscope. Additionally, although significant advances have been made to improve the technology of bronchial navigation devices and real-time imaging modalities, less impressive advances have been made in developing new diagnostic tools.

To be able to improve our ability to diagnose and potential treat small peripheral malignant lung nodules, tools that can maneuver in the close and more angulated environment of the small airways must be developed. Several new needles have been developed to provide enhanced flexible in the smaller airways during greater degrees of articulation. The PeriView FLEX TBNA 21 -G (Olympus) and Arc point (Medtronic) 21 and 18 G- needles are examples. The GenCut core biopsy system (Medtronic) is another example of a more flexible tool that may help provide higher diagnostic yield in the smaller airways. However, the clinical usefulness of these tools needs validation. Overall, our ability to treat a lesion depends on our ability to reach it, and then fully access it. More tools that can allow us to achieve those goals are needed.

Navigational and biopsy tools must be studied in clinical settings to determine their effectiveness. The AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education) program evaluated diagnostic yields of different types of bronchoscopy in clinical practice to identify factors that affect diagnostic yield.(269) They found peripheral TBNA improved diagnostic yield but was underused and diagnostic yields of ENB and r-EBUS were lower than expected. Registry data can help prompt better bronchoscopic instruction and tools for community pulmonologists.

Another area with clear potential for development for minimally invasive procedures in the lung is Natural Orifice Transluminal Endoscopic Surgery (NOTES). NOTES describes a wide spectrum of procedures that uses natural luminal access such as transgastric or transvaginal routes, but could have applicability for other organs, like the lung via the bronchoscope. (270) Since Phillipe Mouret of France performed the first laparoscopic cholecystectomy in 1987 (271),

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NOTES has been studied in the mediastinum; predominately porcine models. Concerns regarding complications of transtracheal or esophageal mediastinoscopy, such as infection and bleeding and healing of the esophageal incision have limited progress. However, this technique could have potential for the diagnosis and treatment of select pulmonary lesions. Further study is required as NOTES techniques evolve.

Summary

A foreign body removed by G. Killian in 1896 was the first bronchoscopy that was subsequently followed by Chevalier Jackson, I. Kubo and others who further advanced bronchoscopic techniques. In the 1960's, S. Ikeda introduced the flexible bronchoscope as a diagnostic tool and in the 1970's, laser and stents fostered the growth of interventional bronchoscopy. With new options, new uses for interventional bronchoscopy are emerging and it's plausible that interventional pulmonology has enormous potential to provide safe and effective diagnostic and therapeutic procedures at reduced costs for many patients with a variety of lung disorders.

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Navigational Techniques		Imaging Assessment of Lung lesions		Accessing Lung lesions		Inspection of Lymph Nodes		Assessment of Mucosal lesions	
Technique	**Pro/Con**	**Technique**	**Pro/Con**	**Technique**	**Pro/Con**	**Technique**	**Pro/Con**	**Technique**	**Pro/Con**
EMB)	Navigation aid	***HRCT***	Enhanced imaging	***Transbronchial Needle Aspirate***	Readily available/cost effective	***EBUS***	Readily available/cost effective	***OCT***	In vivo cellular morphology
	Increased costs, special equipment and training		increased cost and radiation exposure		Insufficient DX tissue and complications of PTX and bleeding		Equipment and disposable costs and training		Investigational, unclear benefit
VBN	Navigation aid	***Radial EBUS***	Noninvasive Endobronchial Imaging	***Transbronchial Lung biopsy***	Readily available/cost effective	***EBUS with mini forceps***	Greater tissue volume	***CLE***	In vivo cellular morphology
	Increased costs, special equipment and training		Special training and equipment required		Insufficient DX tissue and complications of PTX and bleeding		Insufficient clinical data, disposable cots and training		Investigational, unclear benefit
Thin bronchoscopy with guide sheath	Peripheral access	***Fused flouroscopy***	Real-time visualization	***Cryobiopsy***	Greater tissue volume avoids crush artifact	***Elastography***	Noninvasive assessment of LN stiffness	***Image enhancement***	In vivo cellular morphology
	Insufficient DX tissue, special disposables and diagnostic tools		Special equipment, increased cost and radiation exposure		Insufficient DX tissue and complications of PTX and bleeding		Insufficient clinical data, increased equipment costs		Investigational, unclear benefit
Ultrathin bronchoscopy	Peripheral access	***CT Bronchoscopy***	Real time visualization	***TPNA***	Access extraluminal lesions	***CT Bronchoscopy***	Enhanced imaging	***Radial EBUS***	Noninvasive Endobronchial Imaging
	Insufficient DX tissue, special disposables and diagnostic tools		Limited access, increased cost and radiation exposure		Insufficient DX tissue and complications of PTX and bleeding		Limited access, increased cost and radiation exposure		Needs clinical data
Robotic bronchoscopy	Peripheral access/stability	***CBCT + Augmented flouroscopy***	Real-time visualization	***Thin-EBUS***	Noninvasive lung imaging	***Thin-EBUS***	Interlobar LN Real-time imaging	***Thin-EBUS***	Noninvasive Endobronchial Imaging
	Increased equipment costs, special disposables and diagnostic tools		Limited access, increased cost and radiation exposure		Investigational, unclear benefit		Investigational, unclear benefit		Investigational, unclear benefit

Table 1. Overview of Bronchoscopic Diagnostic Tools with Advantages and Disadvantages

Definition of abbreviations: HRCT, high resolution chest CT; EBUS, endobronchial ultrasound; PTX, pneumothorax; OCT, Optical coherence tomography; CLE, Confocal laser endomicroscopy; CBCT, cone beam CT; DX, diagnostic; EMB; electromagnetic bronchoscopy, VBN, Virtual bronchoscopic navigation; TPNA, transparenchymal nodule access

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Table 2. Overview of Advantages and Disadvantages of Current and Potential Flexible Bronchoscopy Therapeutic Tools

Malignant Solitary Nodules and Lesions		**Emphysema**		**Asthma**		**COPD**				**Large Airway abnormalities**	
						Chronic Bronchitis		**Exacerbation**		***Expiratory Airway collapse***	
Radiofrequency Ablation	Treat cancerous SPN	**Endo-bronchial valves**	Lung volume reduction	**Bronch-ial Thermo-plasty**	Improve symptoms, reduce exacerbation	**Rheoplasty** [2]	Improve symptoms, reduce exacerbation	**Total Lung Denervation**	Improve symptoms, reduce exacerbations	***Tracheo-Broncho-malacia***	Tracheal Patency
	Under investigation		PTX, exacerbation		Multiple procedures, exacerbation, PNA,		Under investigation		Under investigation		Granulation tissue and increased secretions
Microwave Ablation	Treat cancerous SPN	**Thermal Vapor ablation**	Lung volume reduction	**Total Lung Denerva-tion**	Improve symptoms, reduce exacerbation	**Liquid Nitrogen Metered Cryospray**	Improve symptoms, reduce exacerbation			**Airway Stenting**	Tracheal patency
	Under investigation		Exacerbation		Under investigation		Under investigation				Granulation tissue and increased secretions
Thermal Vapor Ablation	Treat cancerous SPN	**Lung Coils**	Lung volume reduction			**Micro-debrider**	Improve symptoms, reduce exacerbation				
	Under investigation		Under investigation, Exacerbation, PNA				Under investigation				
Cryoablation	Treat cancerous SPN	**Polymeric agents**	Lung volume reduction								
	Under investigation		Under investigation, Exacerbation, PNA								
Debridement (Laser, Electrocautery, Argon Plasma Coagulation, Microdebrider)	Treat cancerous lesions									***Bronchial and Segmental Airway Stenosis***	
	Special hardware, disposables and training, bleeding,										

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	perforation, airway fire										
Brachytherapy	Treat cancerous SPN									**Bronchoplasty**	Airway Patency
	Need for trans laryngeal catheter										Need for repeat procedures
Chemo injection	Treat cancerous SPN									**Airway Stenting**	Airway patency
	Under investigation										Granulation tissue and increased secretions
Photodynamic Therapy	Treat cancerous lesions									**Electrocautery**	Airway patency
	Under investigation										Need for repeat procedures, cartilaginous injury
Airway Stenting	Airway patency										
	Granulation tissue and increased secretions										

Definition of abbreviations: PNA, pneumonia; PTX, pneumothorax

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Figure 1. A radial EBUS probe in the center of a SPN.

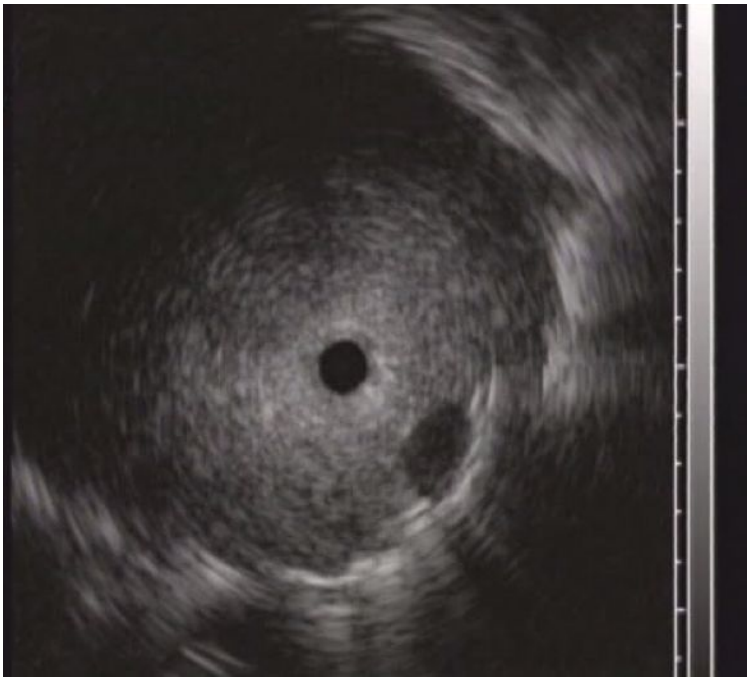

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Figure 2. Overlaid track from the VBN navigational pathway (right side) onto the bronchoscopic image (left side)

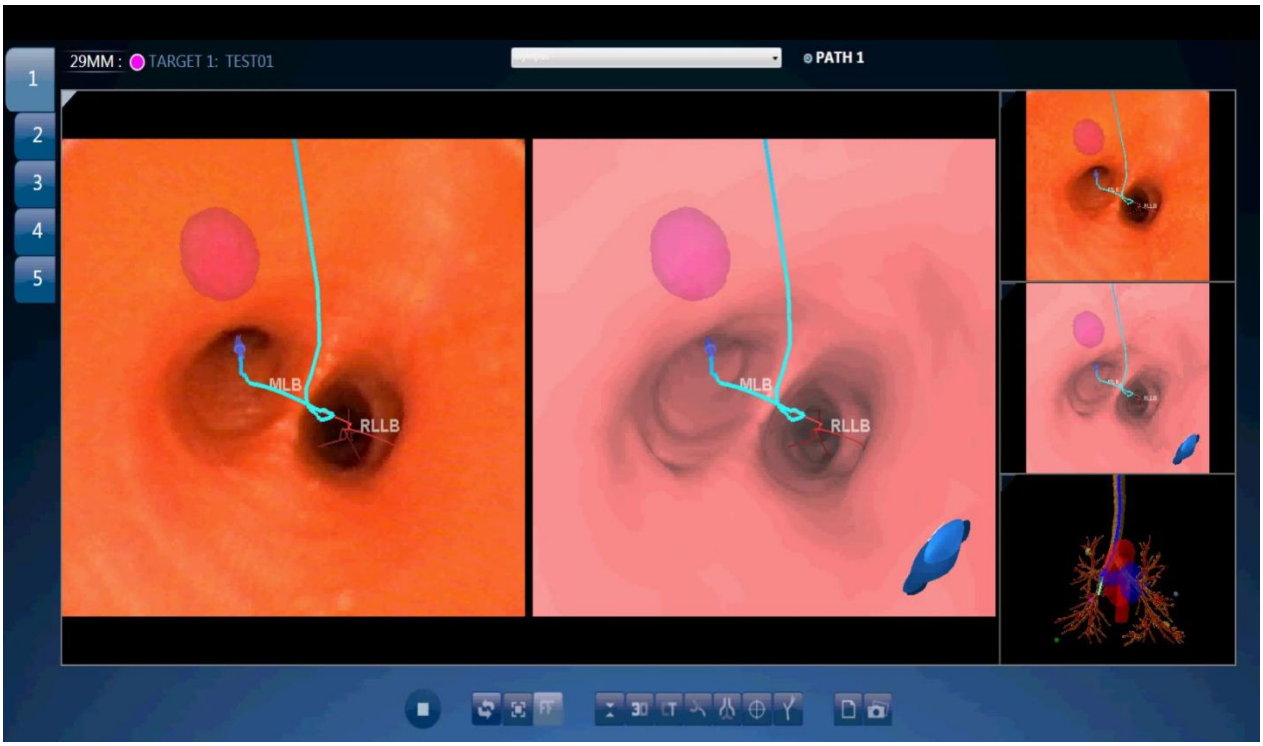

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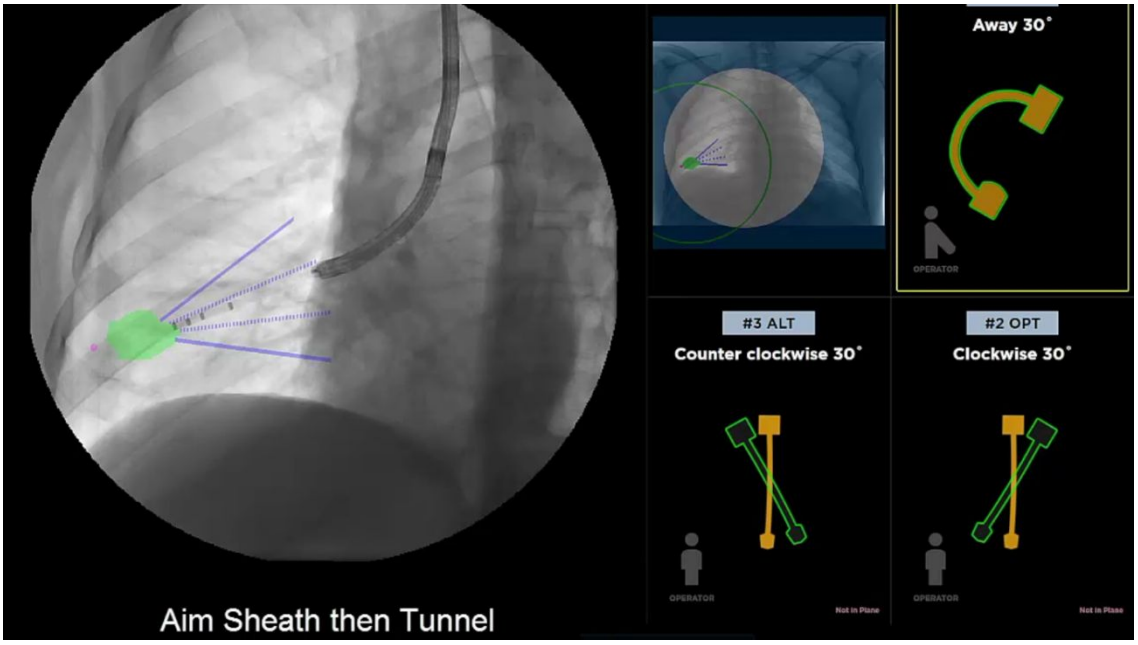
Figure 3, Panel A. View of Transparenchymal Nodule Access (TPNA) on an SPN in the RLL. Fused fluoroscopy is being used to create a fluoroscopically guided transparenchymal path to the superimposed target previously identified by planning HRCT. Purple dot represents virtual pleura. Multiple C-arm projections are used to confirm target location.



Panel B. Three-dimensional (3D) map shows the danger zones and exit point, and the target lesion are demonstrated. (Bowling AnnTS 2017;104: 443-339.)

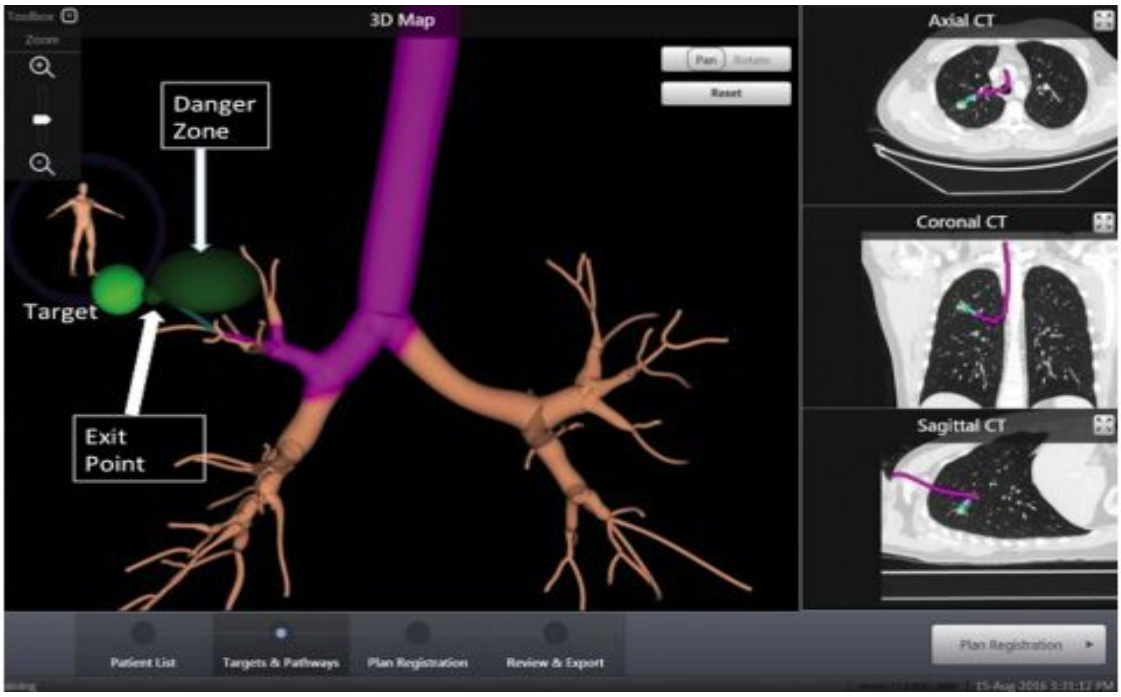


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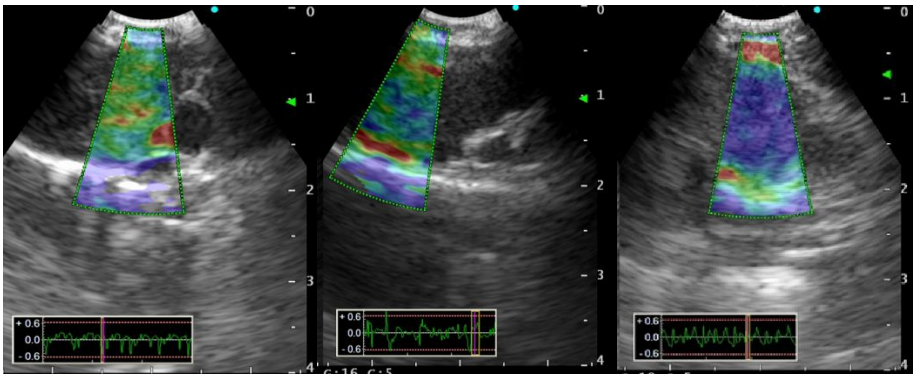
Figure 4. A. Type 1 elastography pattern (homogenous green) in patient with tuberculosis. B. Type 2 elastography pattern (mixed color pattern) in patient with sarcoidosis C. Type 3 elastography pattern (homogenous blue) in patient with adenocarcinoma.



A. B. C.

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Figure 5. Overview of Survival and interventional therapies for advanced emphysema. (Modified from Vogelmeier AJRCCM, 2017)

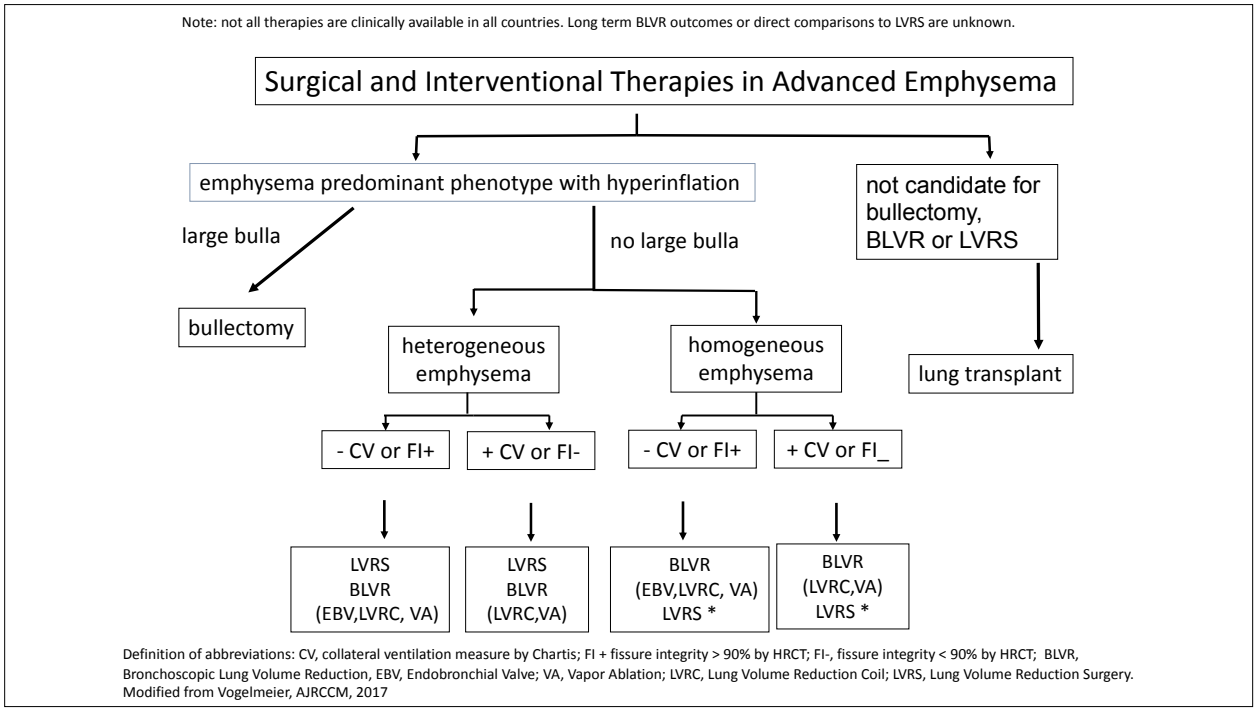

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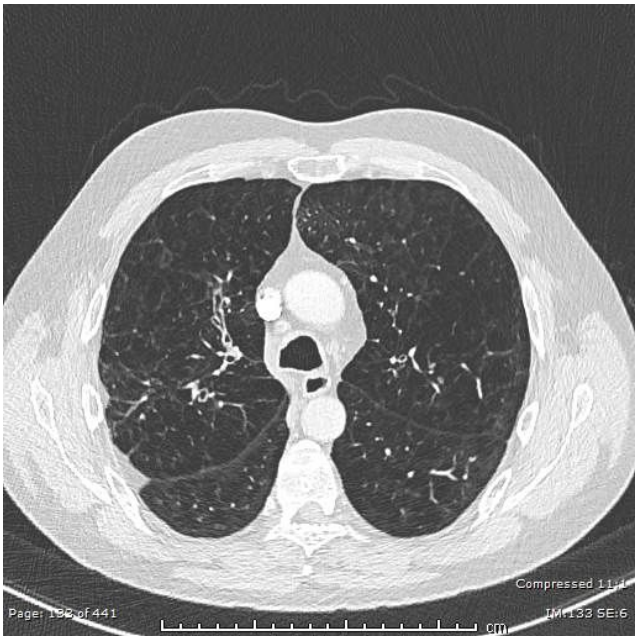
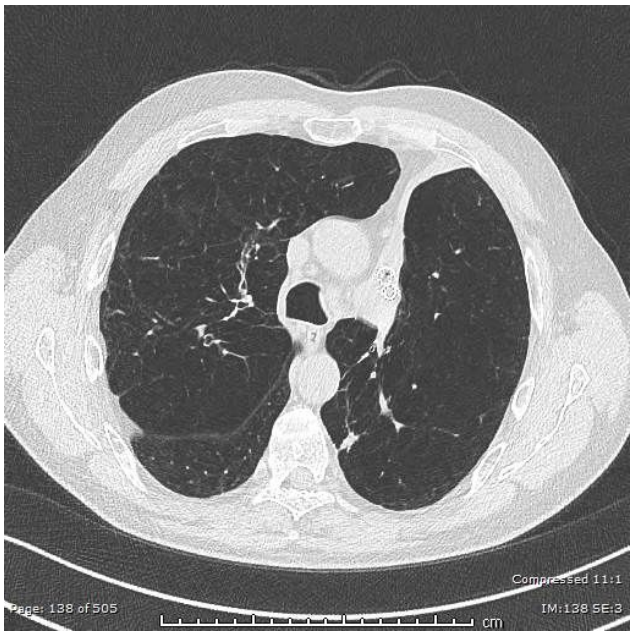
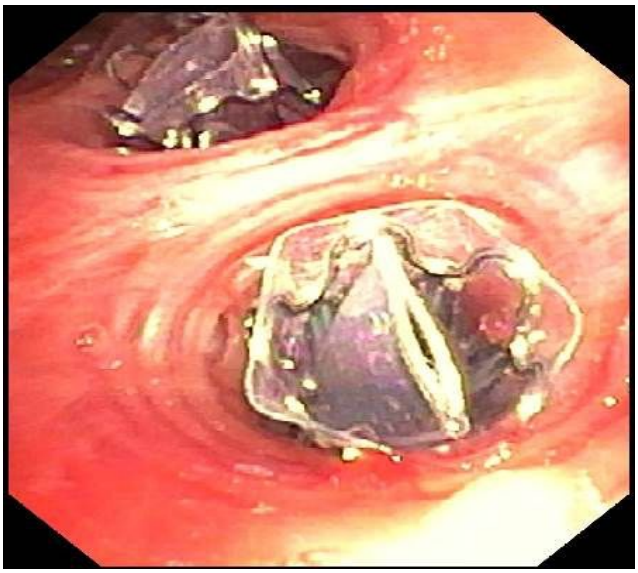
Figure 6. Patient with advanced upper lobe emphysema before (A) and after endobronchial valve placement (B) in LUL showing total lobar occlusion and complete atelectasis. Valves are seen in panel C. Other EBV option (SVS, Spiration, Inc, Seattle WA.) shown in panel D.

A.

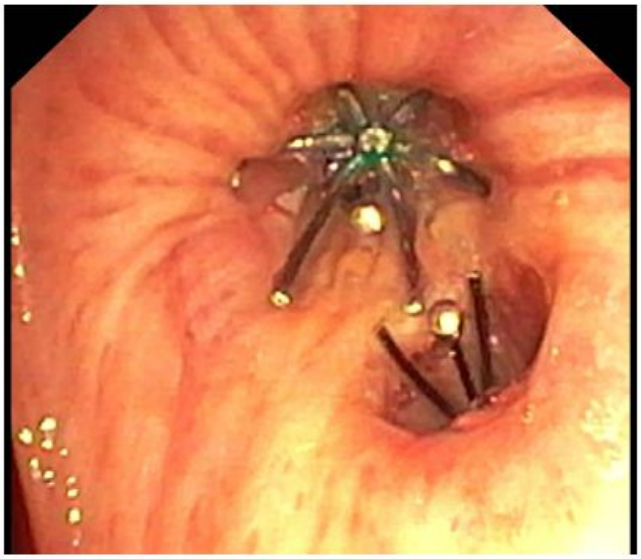


B.





C.



D.

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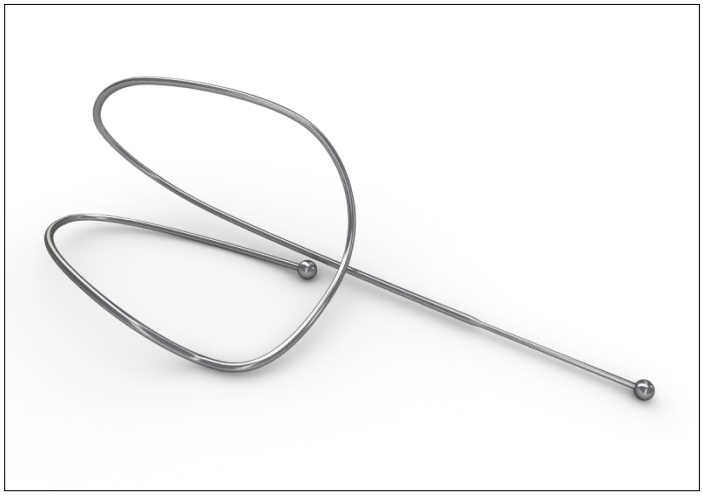
Figure 7. Panel A. Nitnol lung volume reduction coil. Panel B. Coil deployed in lung.



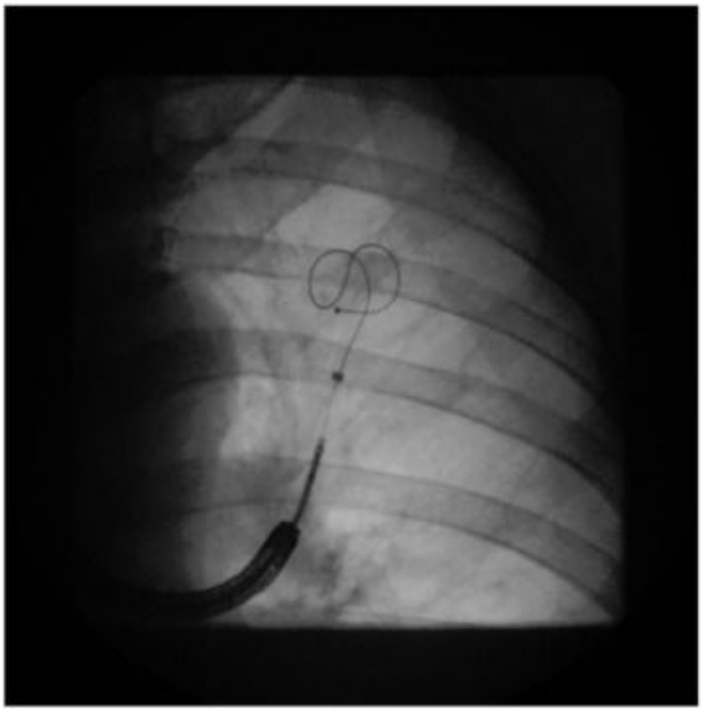


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Figure 8. Total Lung Denervation. Electrode positioned into the distal mainstem bronchi to deliver ablation treatment with thermal insulation provided to airway wall by water cooled jacket.

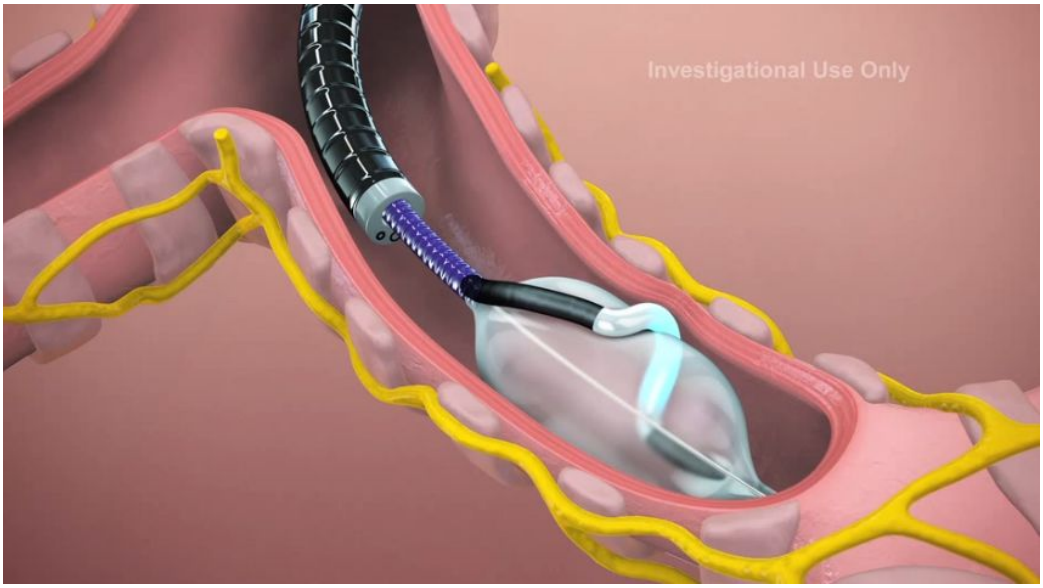

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Figure 9. Rheoplasty. Expanded basket provides airway contact to deliver pulsed field energy to ablate airway epithelial goblet cells.

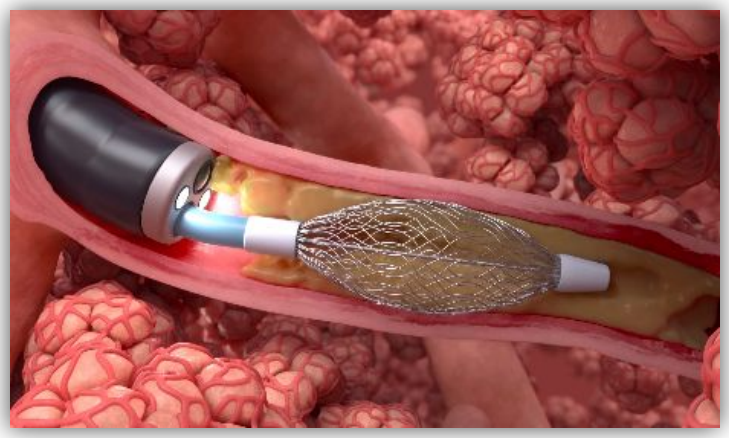

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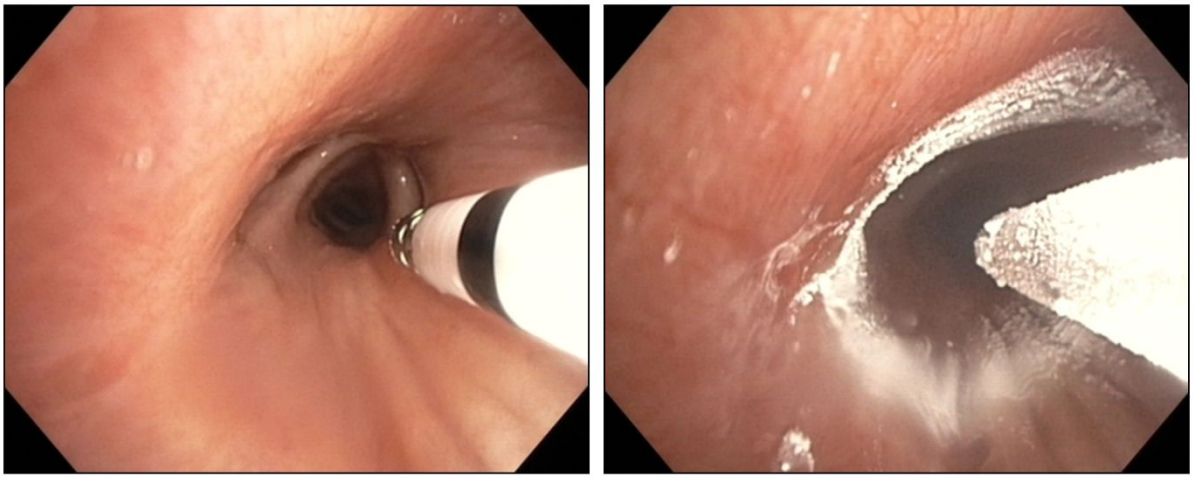
Figure 10. The Rejuvenair Liquid Nitrogen Metered Cryospray. Left panel: Bronchus intermedius with Rejuvenair catheter in situ just before treatment. Right panel: Liquid Nitrogen Metered Cryospray in action at the same position showing the desired circular freezing pattern.



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